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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : G01N 31/00, 33/00, 33/44

A1

(11) International Publication Number: WO 96/21859

(43) International Publication Date: 18 July 1996 (18.07.96)

(21) International Application Number: PCT/US96/00094

(22) International Filing Date: 11 January 1996 (11.01.96)

(30) Priority Data:
08/371,543 11 January 1995 (11.01.95) US

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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AT, BY, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHODS FOR PRODUCTION OF LARGE CATALOGUED CHEMICAL LIBRARIES

(57) Abstract

The invention provides catalogued chemical libraries containing a multiplicity of reaction products and that are useful for screening for a variety of uses including for pharmacological activity, providing pharmacological leads, optimization of lead selection, screening for herbicides, pesticides and the like. The chemical libraries are produced by semi-automated and automated solution chemistry methods and have a cataloging system using an electronic database which allows ready storage and access to a variety of useful information about any of the reaction products.

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METHODS FOR PRODUCTION OF LARGE CATALOGUED CHEMICAL LIBRARIES

Field of the Invention

The invention relates to the production of large catalogued libraries of reaction products for use, for example, in screening for pharmacological activity, providing pharmacological leads, and optimization of lead selection. More specifically, the invention provides methods for producing such libraries having a plurality of reaction products using solution-phase chemistry, and also provides an electronic database so that individual reaction products may be readily identified and characterized by their structure.

Background of the Invention

Traditionally, new medicinal/chemical lead structures have originated from the isolation of natural products from microbiological fermentations, plant extracts, and animal sources. Further, structures have also been obtained through the screening of pharmaceutical company compound databases, and more recently, through the application of both mechanism-based and structure-based approaches through rational drug design.

However, when conventional organic chemistry procedures are used to prepare organic compounds for pharmacological leads or activity screening, the cost per compound is high. For example, a chemist may typically produce between 50 and 100 purified compounds per year through conventional methods. This means that the cost per compound is in the range from $2,250.00 to $4,500.00 (assuming a conservative annual cost for chemist, including overhead, of $225,000.00). Because only a very small proportion of the total number of chemical compounds produced are

found to have pharmacological uses, the cost per useful compound is even higher. Therefore, there exists a strong identified need to reduce the cost per chemical compound produced.

Furthermore, when a particular chemical compound is found to have pharmacological activity, it is desirable to know the chemical structure of the compound so that related compounds, with slightly varying structures, may be investigated in order to select the composition with the optimal pharmacological activity. Thus, it is desirable for a chemical library to offer not only the chemical compound itself, but also the structure of the compound.

Furthermore, once pharmacological activity has been established, typically from a very small sample taken from a chemical library, then further testing requires knowledge of the substrates and reactants, including reaction pathway, necessary to produce larger quantities of the active compound. Consequently, there is a need for information related to the synthesis of the compound to facilitate subsequent testing.

From an organizational standpoint, the information regarding the structure of the active organic compound, the chemicals used in the synthesis of the compound, the reaction pathway, and any other information that a chemist might find useful, should desirably be rapidly and easily accessible.

The development of automated techniques for screening of very large quantities of organic compounds for pharmacological activity, and for use as drug leads, has created a need for very large chemical libraries of compounds that fall within the predetermined class of compositions that must be tested. Also, the very size of these libraries creates a need for an efficient mechanism for cataloguing information regarding the synthesis, structure, and any other useful characteristic, of each compound in the chemical library so that the research chemist may readily access this information.

Summary of the Invention

The invention provides highly efficient methods for producing very large chemical libraries, especially chemical libraries of relatively small organic compounds. Typically, such libraries find use in pharmacological activity screening, as pharmaceutical leads, in agricultural chemistry for testing as herbicides or pesticides, in food chemistry for use in flavors or fragrances, and the like. Despite the large number of different compounds produced by the methods of the invention in the form of reaction products, there is a very high level of reliability that a particular compound is present in a reaction product catalogued in the library because the methods of the invention use well-recognized solution chemistry for synthesis. Further, the chemical

libraries of the invention are accompanied by a coding and tracking system that enables the ready identification of the compound present in any of the large number of reaction products, along with its chemical structure, method of synthesis, substrate and reactants used in the synthesis, and other useful data.

According to the invention, there is provided a method for producing a library of reaction products for screening for pharmacological activity. In this method, the predetermined class of compounds to be screened for pharmacological activity is first established. Then, the method requires selecting at least one substrate able to produce reaction products that fall within the predetermined classes, when the substrate is reacted with reactants. A plurality of reactants, able to react with the substrate, to produce reaction products in the predetermined classes of compounds, is selected. A reaction pathway for reacting each of a multiplicity of individual samples of the substrate with at least one of the plurality of reactants, to produce a multiplicity of reaction products, is determined. A reaction matrix for combining each of the samples of the substrate with an amount of a reactant through the selected reaction pathway is then developed.

At this point, the invention provides for preparing a plurality of separate samples of the substrate and combining a predetermined amount of each of the reactants with a separate sample of the substrate, in accordance with the reaction matrix developed. Desirably, these separate samples of the substrate are placed in separate vials, which are held in trays, able to hold many vials, placed upon shakers, so that the multiplicity of individual substrate samples with added reactant all simultaneously undergo reaction through desired reaction pathways.

Upon determining that the reaction has proceeded to the extent required, the reactions in each of the separate vials are quenched by adding a quenching agent. Thereafter, according to the invention, reaction products are extracted from the quenched solutions using a solvent. The extract produced, containing the reaction products desired, are each distributed into individual storage containers. Samples are then taken from each of these individual containers and redissolved in a suitable solvent in a sample container. The solvent is then removed from the sample product to produce dried reaction products ready for use in pharmacological activity screening.

It should be noted that, according to the method, a reaction matrix may include, for example, x substrates, each of which must be reacted with y reactants, through a number of pathways, such as z pathways. As a result, the total number of reaction products in the chemical library would be the product of x, y, and z.

According to the invention, this multiplicity of reaction products is rapidly and efficiently produced by the synthesis method summarized above, and describe in more detail below.

In order to readily identify each reaction product in the chemical library, the invention provides a method of identification and an electronic database of information that supplies the chemical structure of the compound in the reaction product, and its method of synthesis, including substrates and reactants. To facilitate identification, before the chemical library is created, each of the substrates and reactants are physically labeled with a machine-readable code, such as a bar code which may be readable by a laser reader. Reaction products formed are also tagged to allow subsequent identification of the chemical compound present, its chemical structure, substrate and reactant used to produce the reaction product, as well as the reaction pathway.

The reaction matrix, which includes the structure of the organic compound present in each reaction product, and the substrate and reactant used in making the reaction product, together with the reaction pathway, is retrievably stored in an electronic database. Thus, once a reaction product has been identified as useful, its chemical structure and other particulars may readily be accessed from the database.

The invention also provides a method for producing a chemical library for providing or optimizing pharmaceutical leads. These libraries are created in substantially the same manner as the screening libraries discussed above, except that the selection of substrate, reactants, and chemical pathways is determined by other factors. Thus, libraries of chemical leads are generally focused around a particular chemical that has already been found to have pharmacological activity and the development of other compounds with functional groups and structure varying to a limited extent from the known active compound. The method of identifying individual reaction products of the chemical library is the same as for the screening library.

Detailed Description of the Preferred Embodiments

The combinatorial organic synthesis method of the invention for producing large chemical libraries is especially useful for use in pharmacological screening, and the provision of pharmacological leads or the selection of optimum leads, although other applications are also feasible. Preferably, the organic compounds produced as reaction products have molecular weights in the range from about 200 to about 500 daltons, although larger or smaller compounds may also be produced. Further, the invention also provides for the production of libraries of peptide-like compounds.

In the claims and specification, the term "reaction product" refers to a relatively unrefined product of the reaction of a selected substrate with a selected reactant through a selected reaction pathway, which after one step of purification, such as solvent extraction, produces predominantly a desired chemical compound. Thus, while the desired chemical compound is present in the reaction product, it is usually not present in highly purified form. However, it is within the scope of the invention to purify the reaction products to produce the desired chemical compound.

While the following discussion focuses primarily on chemical libraries for use in the pharmaceutical industry, it will be appreciated that the same procedures may be used to develop such libraries for other applications where screening of a multiplicity of compounds for certain properties is useful. For example, for herbicide or pesticide selection, food fragrances and flavor selection, and the like.

The chemical libraries of the invention may be divided into two types, for ease of explanation. In the first instance, for example, the chemical libraries may be developed for initial pharmacological lead identification. In this embodiment of the method of the invention, the molecular structural objective is undefined, except that the resultant chemical compound should be pharmacologically active. In general, to provide a library for initial lead identification, it is desirable to incorporate a flexible synthesis strategy with diverse building blocks and a variety of reactions or reaction orders into the methodology. The production of "free" compounds (not coupled to solid supports) is favored, although certain biological assays will accommodate compounds that are coupled to solid supports. Because of the large number of samples that must be screened to find a lead, a low cost per sample is desirable.

Alternatively, for lead follow up, in order to develop, for example, a more optimal pharmacologically active compound, the chemical library must be more focused and the molecular diversity of the library is consequently more restricted. To develop such a library, according to the invention, a more focused synthesis strategy is employed using specific building blocks and specific reactions and reaction orders. A free compound is almost always preferred for lead follow up, and a higher cost per sample is tolerated, because some biological activity has already been identified.

It is important to note that the chemical methods according to the invention use solution-phase chemistry. This type of chemistry offers the advantage of being well understood and therefore predictable, so that a large number of reaction products can be produced with a higher level of confidence that the desired chemical compounds are present in the reaction products. Thus, for quality control purposes according to the invention, only about five to about ten percent of the reaction

products produced need be sampled to ensure that the entire library meets the objectives set forth in the reaction matrix.

A further advantage of the invention is that each reaction product is produced separately, in a small reaction vial container and samples of each can subsequently be transferred, for testing, to an even smaller container, such as a well in a microtiter plate. Thus, once activity has been established, the reaction product is readily identifiable, both because it is separate and also because of the identification, cataloguing, and tracking methodology of the invention.

According to the invention, a method of producing a chemical library for pharmacological activity testing proceeds with first determining the class of compounds to be tested for activity. Once the class or classes of compounds have been determined, a substrate, or substrates, are selected that are able to produce compounds within the predetermined class or classes, when each are reacted with a reactant. Reactants are then selected to react with the selected substrate, or substrates, through at least one, and possibly more, reaction pathways to produce reaction products in the predetermined classes of compounds.

At this point, a reaction matrix is developed for combining substrate with reactant through a reaction pathway, or pathways, to produce the reaction products. Thus, the reaction matrix is, for example, as follows:

$$A_{mn} + B_{pn} = (A_m B_p)_n \qquad (1)$$

Where m is the number of substrates A, p is the number of reactants B, and n is the number of reaction pathways. Thus, according to the above reaction matrix, a total of mnp reaction products will be formed. In some instances, the reaction product may not be AB, as shown but A' and a byproduct. For example in reactions that make cyclic compounds from linear substrates through use of another compound, which may be altered to form a byproduct or which is a catalyst. Also, either the substrate or the reactant may be the reaction product of a prior chemical library, according to the invention.

Once the reaction matrix has been developed, according to the invention, the reaction matrix may be entered into an electronic database which will then uniquely identify for each reaction product at least the substrate, reactant, and chemical pathway for producing the reaction product. Also, since the reaction product is produced by solution chemistry, the chemical structure of the reaction product is known and is preferably also entered into the electronic database, along with the

aforementioned information. An exemplary database is ISIS, sold by MDL Information Systems of California.

In the following discussion, for simplicity, reference will be made to a single substrate and reaction pathway, although it must be understood that several substrates may be used, and that reaction may take place through several reaction pathways. Nevertheless, the explanation referring to a single substrate and single reaction pathway is exemplary and illustrates the methodology according to the invention which is readily adaptable to more substrates and reaction pathways by a person of ordinary skill in the art.

The selected substrate is tagged with an identifying marking, preferably a bar code that is readable by a laser reader, although other tagging methods may also be used. The reactants are likewise marked, and a code is selected for the reaction pathway selected. This information is also entered into the electronic database, as explained above.

The separate reactions between the substrate and reactants must now be physically performed. In order to carry out these reactions, and produce separate reaction products, separate amounts of solutions of the substrate in a suitable nonreactive solvent must be placed into individual reaction vials. In order to identify these vials, they are either individually marked, or they may be placed within a tray, in an array of rows and columns, so that each vial is uniquely identified by the position that it occupies in the array. In the event that the row and column identifying method is used, then it is only necessary to identify the individual tray by a bar code. Thus, reaction vials may be placed in trays that are each individually marked with a bar code, while each individual vial on the tray is identified by its location by row and column.

Solvents, reactive starting materials, and any additional chemicals such as catalysts, are added to the reaction vials according to the chosen reaction matrix. To facilitate this addition, solution aliquots are preferably made of the reactants so that predetermined needed aliquots are added to each of the plurality of reaction vials, preferably in an automated or semi-automated liquid transfer process.

The multitude of reaction vials, still in their marked trays, are then placed on orbital shakers where they are shaken for a predetermined amount of time according to the reaction matrix in order to allow chemical reaction to proceed to the desired extent for the production of desired reaction products. The manifolds of the shakers that hold the trays or reaction vials may be modified to control the temperature of the

reaction vials within desired limits. Further, the reactions may proceed under an inert atmosphere, such as nitrogen or helium, if desirable or necessary.

After an elapse of sufficient time for the desired reactions to take place, a quenching agent is added to each of the reaction vials. Preferably, the quenching agent is also in solution to facilitate ready automated addition of an aliquot thereof to each of the reaction vials.

After quenching, a preselected extract solvent for the reaction products is added to each of the reaction vials and the reaction product is dissolved in this solvent. The extract, containing the reaction product, is removed from the reaction vial and transferred to storage vials. Typically, if the reaction vials each contain one millimole of reaction product, then four replicate storage vials may each contain about 250 micromoles of reaction product.

Upon redistributing reaction products from reaction vials to storage vials, care must be taken to maintain the tagging and identification system. Thus, the location of storage vials, by row and column in the array of vials on the bar code-marked tray, must be keyed to the location of the reaction vial and the specific tray from which the reaction vial originated.

The storage vials are stripped of extraction solvent and any volatile components using an automated vacuum dryer, such as a Savant Speed Vac made by Savant Corp. Preferably, the reaction products are not subject to heat, or any other condition that may result in decomposition or altering the reaction product.

Preferably, a random sampling of reaction products from the storage vials is analyzed by a reliable method, such as ion spray mass spectroscopy to ensure successful reactions. Typically, from about five to about ten percent of the reaction products should be sampled and tested.

In order to produce a sample of sufficient size for, for example, pharmaceutical use in screening or lead selection, one of the storage vials of each reaction product is redissolved in an appropriate solvent and an aliquot of the solution sufficient to provide about 25 micromoles of reaction product is distributed into a well of a bar-coded microtiter plate, preferably a standard 96-well microtiter plate wherein the wells are arrayed by row and column. This operation, like the other solution transfer operations, can be carried out using a multi-probe automated multi-channel liquid handling system, such as a Packard multi-probe supplied by Packard Instrument Co.

Thereafter, the microtiter plates are stripped of solvent, preferably in an automated vacuum solvent-removing process, taking care not to decompose the reaction product by exposure to heat or other decomposing conditions.

Preferably, although the preferred microtiter plates have 96 wells, reaction product is only placed in about 72 wells, leaving the remaining wells for use by the end user carrying out screening or lead optimization.

Once again, when samples are transferred from the storage vials to the microtiter plate, according to the invention, a record is kept of the location of a particular reaction product on a particular microtiter plate, by row and column of the array of wells on the bar coded microtiter plate, so that the reaction product may be tracked back to the storage vial from which it originated, and thence back to the reaction vial and the original substrate, reactant, reaction pathway, and chemical structure of the desired chemical compound present in the reaction product, as recorded in the reaction matrix.

As explained above, the method of producing a chemical library, according to the invention, is capable of providing a very large number of reaction products. For example, when ten substrates are combined with 100 reactants, through five pathways, then the total number of reaction products produced are $10 \times 100 \times 5 = 5000$. According to the invention, each of these reaction products is identified by row and column of its position on a microtiter plate supplied to a chemical library user and its chemical structure, molecular weight, as well as the original substrate and reactant from which it is made through a particular pathway, is readily accessible from the electronic database.

In certain embodiments of the invention it may be desirable to provide the reaction vials containing reaction products directly to the end user thereby eliminating subsequent steps of transferring to storage vials and thence to microtiter plates. In this instance, the library is also catalogued, as described above, so that reaction products in each vial are uniquely identified.

In other embodiments, instead of preparing reaction product samples of about 1 millimole size in reaction vials, reaction may proceed directly in microtiter plate wells on orders of magnitude smaller scale. In this event, the plates are each bar coded and the location of each reaction product by row and column on each coded plate is recorded in an electronic data base. The reaction products are dried, as described above, by vacuum solvent removal and are then available for the end user.

In yet another embodiment, the methods of the invention eliminate the storage vials and transfer reaction products directly to wells in microtiter plates from the

reaction vials. Again, as before, reaction products are tagged to ensure identification of each product in each well by recording identifying data in an electronic database. In making the transfer of reaction products to microtiter plate well, the reaction products are each extracted from the reaction vial product, the extract is transferred to the appropriate well, and the extract solvent is removed under vacuum.

The following example is intended to illustrate an embodiment of the invention, and does not in any way limit the scope of the invention as described above and claimed herebelow.

Example 1

A chemical library of 600 reaction products of amines and acid chlorides were produced. These products were the result of reacting 60 amines (listed in Table 1) with 10 acid chlorides (listed in Table 2) by a single reaction pathway. Each of the substrates, reactants and reaction pathway were assigned a bar code identifier which was recorded in an electronic database.

In carrying out the procedure according to the invention, samples of each of the substrates were dissolved in an appropriate solvent, anhydrous methylene chloride, to form a solution. Aliquots of each of these solutions were placed in 10 reaction vials to provide 600 reaction vials of substrate, contained in arrays of rows and columns on 50 vial capacity trays, each tray being marked with a bar-code identifier, recorded on an electronic database. The tray bar codes and location of vials by row and column on each tray were recorded on an electronic database.

Ten solutions were prepared from individual samples of each of the ten acid chloride reactants in anhydrous methylene chloride as a solvent, and an aliquot of one of these solutions was added to each of the reaction vials, according to a predetermined reaction matrix, so that each of the ten vials containing a particular amine substrate received an aliquot of a different one of the ten reactant solutions.

The trays containing the reaction vials were each placed on an orbital shaker, and shaken for about 240 minutes. At this point, the reactions were quenched with an aqueous saturated solution of sodium bicarbonate. Reaction product was extracted from each of the reaction vials using anhydrous methylene chloride as an extraction solvent. The extracts, containing the reaction products, were each transferred to storage vials, also contained in arrays on trays marked with a bar-code identifier which was recorded on an electronic database. The reaction product in each storage vial, identified by row and column, was recorded on an electronic database so that it could be traced back to the original reaction vial from which it came. The trays

containing the storage vials were subjected to a vacuum until a dried reaction product was obtained.

In order to prepare the chemical library for use, samples were taken from the storage vials and redissolved in anhydrous methylene chloride as a solvent. An aliquot of each methylene chloride solution containing a reaction product was then transferred to a well of 96-well microtiter plates, noting the position by row and column of each of the reaction products. The microtiter plates were each bar coded and this code together with the row and column location of each reaction product was recorded on an electronic database. The microtiter plates were then subjected to vacuum to remove the solvent and produce a dried chemical library, containing 600 reaction products, each catalogued in an accessible electronic database, distributed in 600 identified wells of 96-well microtiter plates.

In carrying out the above procedure, information regarding the solution-phase reaction was recorded, as described above. This information may be output from the database as shown in the Reaction Summary of Table 3. This reaction summary describes the reaction (amines with acid chlorides), the products produced (amides), the time of reaction (4 hours), the temperature of the reaction (RT = room temperature), the solvent used (anhydrous methylene chloride) and the quantity of each of the substrates and reactants used. Further, the "work up" describes the quench used (saturated aqueous solution of sodium bicarbonate) and that the product was extracted and vacuum dried. Further, the reaction summary also indicates the precautions, if any, that should be taken in view of the substrates and reactants, and the verification method (in this case, MS = mass spectrometry). When samples are taken to validate the presence of the desired compounds in the reaction products, then the validation date is recorded along with a notebook in which the information may be found. The reaction summary also allows for any other pertinent comments regarding the reactions.

An example of the output obtainable from the electronic database for each of the reaction products is shown in Table 4. It should be understood that, for 600 reaction products, 600 such outputs will be generated. Table 4 provides the chemical structure of the reaction product, shown in two-dimensional drawing in the upper left-hand corner of the outputs, substrate identification (Sub ID), and reagent identification (Reag ID), which are bar-code numbers assigned to the substrate and reagent starting materials. The reaction identification is also given, as "Rxn ID." This number correlates to the reaction number given in the reaction summaries, exemplified in Table 3. The reaction center is also identified, as "Rxn Ctr." Physical

characteristics of the reaction product are given, as required, in the space headed "Phys. Charact." The approximate date of synthesis of the reaction product is given under "Syn. Date." The heading "QC" indicates whether the particular sample was one that was tested for quality control purposes. The molecular formula and weight of the theoretical reaction product is given.

In order to facilitate the rapid identification of any of the reaction products, the bar-code number identifying the storage vial plate is given under "Master ID." The space reserved for "Master Column" records the number identifying the location of a particular storage vial according to the column of the storage tray. The row in which the particular storage file is located on the storage tray is given under "Row."

If the reaction product must be identified by the library user from the microtiter plate, then the "client plate ID" records the bar-code number and well location of the reaction product in the microtiter plate. The remaining codes, such as "Client ID," "Project ID," and "Comments" are self-explanatory.

The invention has been described with reference to its preferred embodiments and as being exemplified in the above example. A person of ordinary skill in the art, having read the disclosure, will appreciate modifications and variations that are within the scope of the invention as described above and as claimed hereafter.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

TABLE 1

a,a,a-trifluoromethoxyaniline
3-chloro-2-methylaniline
2-amino-m-cresol
N-ethyl-3,4-(methylenedioxy)aniline
4-amino-m-cresol
dmethyl-1,3-phenylenediamine•2 HCl
N-ethyl-1-naphthalene
1-piperonylpiperazine
4-amino-diethylamino-cresol•2 HCl
1,2,3,4-tetrahydroquinoline
phenothiazine
cyclopentylamine
1-amino-2-propanol
3-aminoquinuclidine•2 HCl
thiazolidine
1-(2-aminophenyl)pyrrole
ethyl-2-amino-4-thiazoleacetate
5-amino-2-methylbenzothiazole•2 HCl
guanine
5-aminoquinoline
methyl-3-amino-2-pyrazinecarboxylate
1-methyl-4-(methylamino)piperidine
4-amino-6-chloro-2-(methylthio)pyrimidine
2-amino-5-trifluoromethyl-1,3,4,-thiadizole
1-(2-pyrimidyl)piperizine•2HCl
2-amino-4-methylthiazole
3-(2-methyl-1,3-dioxolan-2yl)aniline
2-methoxy-4-morpholinoaniline•HCl
5-amino-4-pyrazolecarbonitrile
3,5-bio(trifluoromethyl)aniline
4-aminophenol
N-methyl-p-anisidine
3,4-methylenedioxyaniline
1,4-benzodioxan-6-amine
3,4,5-trimethoxyaniline
1-aminonaphthalene
aminodiphenylmethane
2-amino-4-hydroxy-5-methyl pyrimidine
morpholine
1,2,3,4-tetrahydroisoquinoline
N-ethylcyclohexylamine
bis(2-methoxeythyl)amine
1-methylpiperazine
1,2,3,-trimethyl-6-azobicyclo-octane
furfurylamine
2-amino-4-phenylthiazole.HBr•H_2O
2-aminobenzothiazole
adenine
1-(2-pyridyl)piperazine
6-aminoquinoline
ethyl-5-amino-1-phenyl-4-pyrazolecarboxylate
5-amino-3-phenyl-1,2,4-thiadiozole
aminopyrazine
4-morpholinoaniline
thiomorpholine
N-allyl-p-anisidine
N-(trifluoro-m-tolyl)veratrylamine
3-methyl-3-phenylpiperidine
glutamic acid diethylester
5-amino-2-methoxypiridine

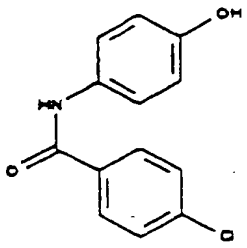
TABLE 2

4-chlorophenoxy acetyl chloride	acetylsalicloyl chloride
4-cyanobenzoyl chloride	3,4-dimethoxybenzoyl chloride
2-thiophene acetyl chloride	o-acetylmandelic chloride
2-furoyl chloride	3,4,5-trimethoxybenzoyl chloride
isonicotinyol chloride•HCl	4-chlorobenzoyl chloride

TABLE 3

RHN Series 3	Description Amines with acid chlorides	Product amides
time 4 hr	temp RT	solvent anhydrous methylene chloride
Equivalent		Workup
1eq. amine, 1.2 eq. acid chloride, 1.4 eq. triethylamine, 4 ml solution/1 mmol amine		aq. sat. sodium bicarb quench, extraction, vacuum dry
Precaution acid chlorides are moisture sensitive, exotherm upon addition of acid chloride		
Verification Method MS		
Validation Date 1/2/94		Notebook
Comment add acid cholorides to amines in solution		

TABLE 4



		Product ID S00126R00129			jgf
		Sub. ID S00126		Reag. ID	R00129
		Rxn.ID 03		Rxn. ctr	amide
		Q.C.			N/A
		Date 10/21/94		Phys. Charact.	
		$C_{13}H_{10}ClNO_2$			247.6830
Master_Id	Master_Column	Master_Row	Client_Plate_Id	Client_Id	Project_Id
M00509	2	all	C00120-B8	101	S79
Comments		1 mmol reaction			

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method of producing a catalogued chemical library of reaction products, comprising:

(a) predetermining classes of compounds to be catalogued in the chemical library;

(b) selecting at least one substrate able to produce reaction products in the predetermined classes of compounds, when combined with at least one reactant;

(c) selecting a plurality of reactants able to react with the at least one selected substrate to produce reaction products in the predetermined classes of compounds;

(d) determining at least one reaction pathway for combining the selected at least one substrate with each of the selected plurality of reactants to produce a multiplicity of reaction products in the predetermined classes of compounds;

(e) developing a reaction matrix for combining individual samples of each of the selected substrates with individual samples of each of the plurality of reactants through the determined at least one reaction pathway to produce the multiplicity of reaction products;

(f) distributing predetermined aliquots of solutions of the at least one substrate into separate reaction vials;

(g) retrievably recording, in an electronic data base, identifying information for each of the multiplicity of reaction products established in developing the reaction matrix, said identifying information comprising chemical composition, substrate, reactant, and reaction vial wherein the reaction product will be formed; and

(h) reacting each of the distributed aliquots of the at least one substrate with a solution of at least one of the plurality of reactants to produce reaction products in the reaction vials.

2. The method of Claim 1, further comprising, after said reacting of step (h):

extracting reaction product from each of the reaction vials with a solvent;

redistributing each of the extracted reaction products into identified separate containers;

removing solvent from the redistributed extracted reaction products to produce dry reaction products; and

retrievably recording in the electronic database, information identifying a specific identified separate container into which each reaction product was redistributed.

3. The method of Claim 2, further comprising:

redissolving reaction products in the identified separate containers, of the redistributing step, in a suitable solvent to form solutions;

transferring aliquots of the solutions to separate identified smaller containers;

drying the transferred aliquots to produce reaction product samples in each of the separate smaller containers; and

retrievably recording, in an electronic database, information identifying a specific identified smaller container into which each of the aliquots was transferred.

4. The method of Claim 1, wherein the step of retrievably recording comprises:

recording a bar code of a tray whereon reaction vials are placed in row and column arrays; and recording the row and column position of each vial, containing reaction product, on the tray.

5. The method of Claim 2, wherein the step of recording information identifying a specific separate container comprises:

recording a bar code of a tray whereon the separate containers are placed in row and column arrays;

and recording the row and column position of each separate container containing reaction product on the tray.

6. The method of Claim 1 wherein the step of reacting comprises producing organic reaction products having a molecular weight in the range about 200 to about 500 daltons.

7. A method of producing a library of reaction products for screening for pharmacological activity or pharmaceutical leads from selected substrates and reactants through preselected chemical reaction pathways, the method comprising:

(a) predetermining classes of compounds to be screened for pharmacological activity or pharmaceutical leads;

(b) selecting at least one substrate able to produce reaction products in the predetermined classes, when chemically reacted with a reactant;

(c) selecting a plurality of reactants able to react with the at least one substrate to produce a multiplicity of reaction products in the predetermined classes of compounds;

(d) determining at least one reaction pathway for reacting samples of at least one substrate with samples of the plurality of reactants to product a multiplicity of reaction products in the predetermined class of compounds;

(e) developing a reaction matrix for combining samples of the at least one substrate with samples of the plurality of reactants through the at least one reaction pathway to produce the multiplicity of reaction products;

(f) retrievably recording, in an electronic database, information from the developed reaction matrix, said information comprising the molecular weight, chemical formula and chemical structure of each of the multiplicity of reaction products, substrates and reactants to produce each of said products, an identifier for a reaction vial wherein each of said reaction products will be produced;

(g) combining, in solution phase, in individual reaction vials, predetermined amounts of each of the plurality of reactants with separate samples of the at least one substrate in accordance with the reaction matrix developed;

(h) quenching reactions in the reaction vials after a period of time required to produce a desired level of conversion to reaction products in solution;

(i) extracting reaction products from quenched solutions with an extraction solvent;

(j) distributing extracted reaction products into individual storage vials;

(k) retrievably recording in the electronic database, information identifying each individual storage vial and the reaction product distributed therein;

(l) sampling distributed reaction products from the individual containers;

(m) redissolving sampled distributed reaction products in a suitable solvent;

(n) redistributing the redissolved reaction products into arrayed wells in a microtiter tray;

(o) retrievably recording, in the electronic database, information identifying each individual well and the reaction product redistributed therein, and

(p) removing the suitable solvent from the redistributed redissolved reaction products to produce a chemical library having a plurality of reaction products for use in pharmacological activity screening.

8. The method of Claim 7, wherein the recording of step (f) comprises recording a unique position of each reaction vial on trays carrying an array of the reaction vials arranged in rows and columns, and recording bar codes identifying the trays.

9. The method of Claim 8, wherein the recording of step (k) comprises recording a unique position, by row and column, of each individual storage vial on trays, each carrying an array of the storage vials arranged in rows and columns, and recording bar codes identifying each tray.

10. The method of Claim 9, wherein the recording of step (o) comprises recording a unique position of a well on microtiter trays, said wells arranged in an array in the microtiter tray in rows and columns, and recording bar codes identifying each microtiter tray.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00094

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 31/00, 33/00, 33/44
US CL :436/8, 85, 86, 89, 91

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/8, 85, 86, 89, 91

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BAUM, Rudy M. Combinatorial Approaches Provide Fresh Leads for Medicinal Chemistry. Chemical and Engineering News. 07 February 1994, pages 20-26., see entire document.	1-10
Y	Advanced ChemTech Bulletin, 1993, 'Combinatorial Synthesis', two pages, see entire document.	1-10
A	GALLOP et al. Application of Combinatorial Technologies to Drug Discovery. 1. Background and Peptide Combinatorial Libraries. Journal of Medicinal Chemistry, 29 April 1994, Vol. 37, Number 9, pages 1233-1251, see entire document.	1-10

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 APRIL 1996	01 MAY 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer P. ACHUTAMURTHY Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00094

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GORDON et al. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screeining Strategies, and Future Directions. Journal of Medicinal Chemistry, 13 May 1994, Vol. 37, pages 1385-1401, see entire document	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00094

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE
Search terms: reaction product, reaction pathway, peptide, polypeptide, library, combinatorial, computer, database, bar codes.